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Structural studies of pravastatin and simvastatin and their complexes with SDS micelles by NMR spectroscopy

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ABSTRACT

Conformational features of pravastatin and simvastatin molecules in solution and in their complexes with sodium dodecyl sulfate micelles (SDS) were studied by 2D NOESY NMR spectroscopy. On the basis of the nuclear magnetic resonance experiments it was established that pravastatin and simvastatin can form molecular complex with SDS micelles which were considered as the model of cell membrane. In addition, interatomic distances for studied compounds were calculated based on 2D NOESY NMR experiments. It was shown that pravastatin interacts only with a surface of model membrane. However, in contrast to pravastatin, simvastatin penetrates into the inner part of SDS micelles. Observed distinctions in the mechanisms of interaction of pravastatin and simvastatin with models of cell membranes could explain the differences in their pharmacological properties.

1. Introduction

Cholesterol-lowering agents, such as pravastatin and simvastatin, participate in the treatment of hypercholesterolemia because of their ability to regulate cholesterol synthesis [1]. These compounds also have profitable actions in many other diseases, such as osteoporosis, cardiac and neurological sicknesses [2]. It is known that the efficacy, metabolism, and safety of statins depend on their location in molecular membrane [3]. The knowledge about mechanisms of interaction of these drugs with cellular membranes can provide a way to explain an origin of their pharmacologic characteristics.

NMR spectroscopy is productive instrument for structural studies of biomolecules [4–10]. Particularly, one of the most effective methods for conformational structure investigations of statins and their complexes with different compounds is nuclear Overhauser effect spectroscopy (NOESY) [2,11–15]. However, there is a disadvantage in applying this technique for studies of interactions in phospholipid membrane because transverse proton relaxation time of phospholipid aggregates is too short relative to the NMR time-scale. Nevertheless, interactions of different drugs with phospholipid bilayers can be effectively investigated by NMR using model membranes. Sodium dodecyl sulfate (SDS) micelles is one of the commonly used membrane models in NMR studies [16–22]. Head polar groups of SDS can be used to physically mimic a surface of biological membrane. Furthermore, SDS micelles are the most convenient model for NMR studies due to their smaller size and larger correlation times relative to the NMR time-scale [23,24]. As a consequence, NOESY experiments provide many information about the mechanisms of interactions of statins with SDS micelles. That is why this model of cell membranes was used in this work.

The aim of our investigation was to study the conformational features of pravastatin and simvastatin molecules and the mechanisms of interaction between statins and model membranes by NMR spectroscopy. We hope that the results presented in this article will help to shed some light on the origin of the physicochemical and pharmacological distinctions of different statins.

2. Experimental section

Pravastatin, simvastatin and SDS were purchased from Sigma–Aldrich Rus (Moscow, Russia) and used without further purification. Pravastatin was dissolved in SDS + D_2O with concentration of 6 g/l. Simvastatin was dissolved in DMSO and SDS + D_2O with concentration of 6 g/l. The concentration of SDS in D_2O solution was greater than critical micelle concentration (8.2 mM) and was equal to 23 mM, diameter of micelle – 5 nm. Solution volume was 0.6 ml,

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